

The Examiner has stated that the priority claim in this application has not been perfected, and accordingly, Applicants are not entitled to claim priority from Provisional Application No. 60/058,258, filed September 9, 1997. In addition, the Examiner has made other formal objections to the specification. Applicants have attended to the Examiner's objections to the specification. Reconsideration and withdrawal are requested.

a. The specification has now been amended to make specific reference to both the PCT application and the prior provisional application. As a result of this amendment, the effective filing date of the present application is September 9, 1997.

b. An Abstract for this application has been added.

c. The Brief Description of the Drawings has been amended in order to provide an appropriate description for FIGS. 1A and 1B.

d. Claims 11, 13, 18, 19 and 23 have been amended to remove certain informalities as noted in the Office Action.

Claims 1, 11, 13, and 15-24 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To expedite prosecution, Applicants have amended the claims to more explicitly point out the claimed OP/BMP morphogens used in the methods of the present invention. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

The Examiner states that the present claims are open to include a large number of possible amino acid sequence variants, and that these variants may not be operable in the context of the invention. However, applicants respectfully submit that simply because a claim is open to include a large number of possible embodiments does not mean that the claim is overly broad or not enabled. The test for enablement is whether the claim is supported by the specification, and no objection has been made that the claims lack support in the specification. Moreover, a limited amount of experimentation is permissible under 35 U.S.C. 112, first paragraph, to determine whether a particular variant is operable. In accordance with MPEP 2164.08(b), "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that

were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.” This standard has been upheld in the courts which have found that a claim may encompass a finite number of inoperable embodiments so long as operable embodiments can be determined using methodology specified in the application. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976).

The claims have now been amended to recite that the claimed morphogens have at least 70% amino acid identity with the C-terminal seven cysteine skeleton of human OP-1. Furthermore, Applicants have provided a functional limitation so that one of skill in the art can readily envision the claimed subject matter. Accordingly, the OP/BMP morphogens used in the methods of the present invention are described in terms of both sequence and functional limitations such that one of skill in the art can readily evaluate the claimed subject matter. Applicants direct the Examiner’s attention to page 11, lines 1-9 and page 11, line 30-page 12, line 9 which provide methods to align OP/BMP morphogens, as well as specific assays to evaluate the function of morphogens and morphogen variants. Accordingly, in Applicants’ view, the scope of the present claims fully satisfies the enablement requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of this rejection are requested.

Furthermore, claim 24 was rejected under 35 U.S.C. 112, first paragraph. To expedite prosecution, Applicants have canceled claim 24 rendering rejection of this claim moot. Cancellation of claim 24 is not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Claims 28 and 29 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement in the specification. The Examiner has stated that these claims, which are drawn to pharmaceutical preparations, are not enabled since the specification is only enabling for *in vitro* processes. This ground of rejection is traversed.

Applicants acknowledge that there is a difference between *in vivo* and *in vitro* methods. However, the Examiner fails to acknowledge that the purpose of *in vitro* experimentation is to model or simulate how a particular treatment protocol would function in an *in vivo* model. In the case of the present invention, there is no sound reason to question that the claimed treatment methods would be efficacious in an *in vivo* model. For instance, pages 18-21 of the specification

set forth typical pharmaceutical formulations and routes of administration which would be operable in the present invention.

Additionally, Applicants have provided extensive evidence in a neuronal culture system to support the enablement of the scope of the present claims. In accordance with MPEP 2164.02, the establishment of strong *in vitro* evidence or *in vivo* evidence obtained in a non-human animal model system is sufficient to make a correlative argument for a claimed *in vivo* method. "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." Applicants have presented evidence which demonstrates that the methods of the present invention have broad applicability. Applicants demonstrate the synergistic effects of administering a combination of OP/BMP morphogens and GDNF/NGF neurotrophic factors to tissues derived from several different regions including the lumbar region, the lumbar-sacral region, the orbit, and the dorsal mesorectum. Accordingly, one of skill in the art would reasonably correlate this data with the general ability of this combination to function in other models. Such correlation need not be exact or rigorous, as asserted by *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed Cir. 1985). "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

Applicants have demonstrated the efficacy of the invention in several model culture system. Applicants cannot be expected to wait for additional laboratory models to spontaneously develop. This sentiment was echoed by the Federal Circuit in *In re Brana*. In addressing whether the invention satisfied the utility requirement, the Court found that the applicants' experimental evidence in a particular tumor model was sufficient evidence of the utility of the invention. Furthermore, the Court pointed out that if scientists were required to wait until animal models for all diseases were developed or occurred spontaneously, there would be no effective way to conduct medical experiments. "If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo*, as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale." (*In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 Fed Cir. 1995). Accordingly, reconsideration and withdrawal are requested.

Claims 1, 11, 13, and 15-24 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by the Bengtsson et al. reference. Applicants traverse the rejection.

Without reviewing the merits of the Bengtsson reference in detail, applicants observe that the effective date of this reference appears to be May 19, 1998, based on the date of acceptance of the paper. However, applicants intend to perfect the priority claim for the provisional application which the present application is based on. After perfecting the priority claim, the effective date of this application will be September 9, 1997. Consequently, the rejection on the basis of this reference will be effectively obviated.

Claims 1, 11, 13 and 15-24 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over the Lein et al. reference in view of the Durbec et al. reference. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as obvious over the Lein et al. reference in view of Durbec et al. and Weiss et al. These grounds of rejection are respectfully traversed.

The Examiner contends that Lein et al. discloses that OP-1 and NGF are cofactors that influence dendritic growth in sympathetic neurons. The Examiner also acknowledges that Lein et al. is directed exclusively to NGF, and is silent on other nerve growth factors, such as GDNF. In order to remedy the shortcomings of the Lein et al. reference, the Examiner has cited the Durbec et al. reference as disclosing the functional interaction between the Ret receptor and GDNF. However, Durbec et al. does not teach or suggest any equivalence between NGF and GDNF as contended by the Examiner. Nor does the Examiner cite any other evidence in the art to establish a structural equivalence between GDNF and NGF.

In particular, Durbec et al. discloses that GDNF has unique properties among nerve factors in that it signals through Ret RTK, and is a distant member of the TGF- $\beta$  superfamily. The reference highlights this uniqueness by emphasizing that GDNF signals through an RTK, while other members of the TGF- $\beta$  superfamily signal through serine-threonine kinase receptors. See pages 791 and 792 of the reference. In contrast, as explicitly pointed out in the specification, NGF is a member of the neurotrophin family. Consequently, there is no basis for concluding that one skilled in the art would be motivated to combine the Lein et al. and Durbec et al. references as suggested by the Examiner. In light of both the specification and the knowledge in the art with respect to growth factors, GDNF and NGF are growth factors belonging to separate

families. Accordingly, there is no motivation to combine the cited references. Reconsideration and withdrawal of this rejection is requested.

The Weiss et al. reference discloses the preparation of pharmaceutical compositions which include various ingredients, including morphogens. However, this reference does not cure the deficiencies of the Lein et al. and Durbec et al. references as noted earlier, as applied to claims 28 and 29. Reconsideration and withdrawal of this reference is requested.

### **CONCLUSION**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Respectfully Submitted,

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